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Emitted dose and lung deposition of inhaled terbutaline from Turbuhaler at different conditions

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Summary

Turbuhaler has a very high resistance hence patient inhalation flow when using it would be low.

The total emitted dose (TED) of 500 µg terbutaline sulphate from a Bricanyl Turbuhaler was determined using a range of inhalation flows (10–60 L min⁻¹) with inhalation volume of 2 and 4 L using a DPI sampling apparatus after one and two inhalations.

The relative lung and systemic bioavailability of terbutaline from Bricanyl Turbuhaler when used by healthy subjects and COPD patients were determined after one and two inhalations at slow and fast inhalation flows using a novel urinary terbutaline pharmacokinetic method.

The TED resulted from the one and two inhalations increased significantly ($p < 0.05$) with the increase of the inhalation flow at both 2 and 4 L inhalation volumes. The relative lung and systemic bioavailability after one inhalation at fast inhalation flow were significantly higher ($p < 0.01$) than at slow inhalation flow in both healthy subjects and patients. Also the healthy subjects results were significantly higher ($p < 0.05$) than the COPD patients after one inhalation.

However after two inhalations there was no significant difference between slow and fast inhalation flow or healthy subjects and COPD patients.

Hence it is essential to inhale twice and as deep and hard as possible from each dose of Turbuhaler for patients with low inspiratory flow and limited inhalation volume as they may not receive much benefit from one inhalation.

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Introduction

All currently marketed dry powders inhalers need internal turbulent energy during inhalation to generate an emitted dose containing particles with the potential for lung deposition. For some dry powder inhalers the dependence of drug delivery on inhalation flow rate is very small whereas for others there is a steep increase in dose emission with the speed of the inhalation flow. The Turbuhaler has previously been shown to be a device of high resistance,¹ which also demonstrates in vitro flow dependent dose emission.² Owing to its high airflow resistance, it is difficult to achieve a peak inhalation flow rate ≥ 60 L min⁻¹ through Turbuhaler. The variation of the emitted dose is a very important factor that could affect the clinical response and side effects. Two gamma scintigraphy studies using radiolabelled short acting β_2 agonist and budesonide in a Turbuhaler showed that total lung deposition can vary with the inhalation flow.^{3,4} All the studies focus on inhalation flow of greater than 30 L min⁻¹ through a Turbuhaler, however during routine use some patients do not achieve that 30 L min⁻¹ required for the delivery of the dose.⁵

Pharmacopoeia tests for dose emission recommend using an inhalation flow equivalent to a pressure drop of 4 kPa across the inhaler with 4 L inhalation volume. This corresponds to a peak inhalation flow rate of 53 L min⁻¹ when using a Turbuhaler.¹ Whereas most COPD patients will inhale around 2 L as inhalation volume and some may even inhale at a very low inhalation flow that cannot produce 4 kPa pressure drops across the inhaler.⁶ To overcome this problem the manufacture leaflet of most of the dry powder inhalers recommend the patient to inhale the dose from the inhaler as hard and deep as possible.

A novel salbutamol pharmacokinetic method has shown that the amount of salbutamol excreted 30 min post dosing is an index of the total lung deposition (lung bioavailability of inhaled dose) and the amount of salbutamol excreted 24 h post dosing is an index of the systemic bioavailability of inhaled dose.⁷ The novel urinary salbutamol pharmacokinetic method⁷ was extended to terbutaline⁸ so that the patient's salbutamol prescription can be maintained. Hence terbutaline dosage form can be used as the study preparation for patient studies.

The aim of this study were to determine the terbutaline sulphate total emitted dose (TED) after one and two inhalations from a Turbuhaler using different peak inhalation flows with inhalation volumes of 2 and 4 L. The generated in vitro data is to be linked to the in vivo fate of terbutaline sulphate from Bricanyl Turbuhaler after one and two inhalations in healthy subjects and COPD patients inhaling at slow and fast inhalation flow.

Method

Total emitted dose

The total emitted dose (TED) was determined using inhalation flows of 10–60 L min⁻¹ and 2 and 4 L inhalation volume using a DPI sampling apparatus (Copley Scientific Ltd, UK) after one and two inhalations.

The dose of 500 μ g terbutaline sulphate emitted from a Bricanyl Turbuhaler was determined using the dose emission method described in the US Pharmacopoeia 2005⁹ except that a range of flows have been used instead of the flow that produces 4 kPa pressure drop across the device. For each determination two dose emission apparatus were used so that the dose emitted from the first inhalation and a second inhalation can be measured separately. The emitted dose in each apparatus was then summed to give the two inhalations TED value.

The emitted dose from the Bricanyl Turbuhaler (labeled as a nominal dose of 500 μ g terbutaline sulphate per puff, AstraZeneca, UK) was measured using a DPI sampling apparatus with a critical flow controller model TPK (Copley Scientific Ltd, UK). The final filter was a 47 mm A/E fiber glass filter discs (Pall Corporation, USA). Vacuum flow through the apparatus was provided by a GAST pump (Brook Crompton, UK). The standard compendial methodology of the USP at an inhalation volume of 4 L and at pressure drop of 4 kPa was modified to allow determination at different flows and volumes. The inhalation flow through the mouthpiece of the Turbuhaler was set at 10, 20, 30, 40, 50 and 60 L min⁻¹ with flow-duration of 24, 12, 8, 6, 4.8 and 4 s respectively to allow an inhaled volume of 4 L of air to be drawn through the inhaler and 12, 6, 4, 3, 2.4 and 2 s respectively to allow an inhaled volume of 2 L of air to be drawn through the inhaler. The flow was measured by an electronic digital flow meter (MKS Instruments, USA). Parafilm M laboratory film (Pechiney Plastic Packaging, USA) was used to seal the apparatus.

Each inhaler was inserted tightly into the mouthpiece and aligned along the horizontal axis. The emitted dose from the Bricanyl Turbuhaler was measured by collecting one individual dose at different inhalation flows. For each determination the Turbuhaler was loaded to deliver a dose, according to the instructions in the patient information leaflet. For each inhalation flow, the emitted dose of 10 separate, single doses, throughout the life of each inhaler, were determined ($n = 10$). For this procedure a switching system was used to produce sonic flow conditions, as recommended by the Pharmacopoeial Methods.^{9–11} Doses not required were discharged to waste using a flow of 90 L min⁻¹ for a 16 s vacuum period to clean the Turbuhaler. This flow has been reported to clear the Turbuhaler from residue.¹² Following dose emission into the apparatus, the sampling unit was washed with 25% acetonitrile and the filter was completely submerged in 25% acetonitrile and then sonicated for 3 min (preliminary analysis revealed that this procedure removes all drug entrained on the filter). The amount of drug was determined by high performance liquid chromatography. The method used was a Water Spherisorb C18, ODS1 column through which a mobile phase of 5 mM potassium dihydrogen orthophosphate-acetonitrile (75:25), adjusted to pH 2.5 with orthophosphoric acid, was pumped at 1 ml min⁻¹. The spectrofluorometric detector (RF-551, Shimadzu, Japan) was set at an excitation/emission of 267/313 nm and bamethane hemisulphate (Sigma, UK) was the internal standard. The limit of detection was 10.9 μ g L⁻¹ and the lower limit of quantification was 33.1 μ g L⁻¹. The total dose emitted was the amount deposited in the plastic dose sampling apparatus and the final filter.

In vivo procedure

The study was a four-way cross-over on 4 different days with 7 days washout period (one inhalation fast flow, one inhalation slow flow, two inhalations fast flow, two inhalations slow flow), with a total dose of 1000 µg of terbutaline sulphate on each occasion.

An ethical approval was obtained from the University of Beni Suef for the health subjects study and all volunteers gave signed informed consent. Twelve healthy non-smoking volunteers (six females), older than 18 years with a mean FEV₁ > 90% of predicted, agreed to inhale two doses through two Bricanyl Turbuhalers (labeled as 500 µg terbutaline sulphate nominal dose, AstraZeneca, UK), using slow and fast inhalation flows.

A local hospital research ethics committee approval was obtained for the patients study. COPD patients, with FEV₁ less than 50% of predicted at screening, were asked to take part in this study. If they accepted to take part in the study, consent was obtained from each patient. If at any time the patient requested to quit the study then they were withdrawn together with all their data and their samples were disposed. For each patient, the FEV₁ was measured on the study day before taking the dose resulting in four FEV₁ for each patient.

The healthy subjects and the patients were trained how to inhale using a slow inhalation flow (30 L min⁻¹) and also a fast inhalation flow (60 L min⁻¹) with aid of the In-Check Dial. They all received training on how to use a Turbuhaler. Doses were loaded for the subject before use according to the patient information leaflet. Subjects were trained to breathe out gently but not breathe out through the inhaler, prepare a dose for inhalation as recommended in the patient information leaflet, then place the mouthpiece between their lips and inhale through their mouth, according to the inhalation flow to be used. Inhalation continued till their lungs were full (total lung capacity) and they then removed the Turbuhaler from their mouth and held their breath for 10 s before breathing out slowly followed by normal breathing. Each subject inhaled two doses from two separate Bricanyl Turbuhalers using either a slow or a fast inhalation flow maneuvers in random order.

The use of the two Turbuhalers was to avoid the inhalation of the residual part that would remain in the Turbuhaler from first dose. The residual part was later removed from the Turbuhaler by discharging to waste using a very high inhalation flow (90 L min⁻¹) for 16 s. This testing maneuver was to measure the bioavailability of one inhalation.

To do a two inhalations test, the patient was asked to do the same maneuver of one inhalation at slow and fast inhalation flow but inhale twice from each inhaler.

On each study day subjects were allowed to have a light breakfast and no caffeine or alcohol containing drinks for at least 12 h before dosing. According to the novel urinary terbutaline method,⁸ immediately before each study dose each subject voided their urine then provided a urine sample 30 min after the start of the first dose and cumulatively collected their urine for 24 h. The volumes of urine samples were measured and assayed for the urinary terbutaline concentration using an HPLC-fluorescence spectrophotometry. The terbutaline was extracted from the urine samples together with Bamethane (Sigma, UK) as internal standard using solid phase extraction, Isolute HXC 130 mg 10 ml XL cartridge and Oasis HLB 30 mg cartridge, then injected in the HPLC system. The method used was an ODS 5 µm, (4.6 × 250 mm, Zorbax, Phenomenex) C-18 HPLC column with a (4 mm × 3 mm, Phenomenex); C-18 (ODS) guard column. Both were maintained at 30 °C. The mobile phase was acetonitrile–methanol–tetrahydrofuran–ethyl acetate–buffer 5:5:5:5:80% v/v. The buffer was 40 mM phosphate buffer and 27.5 mM sodium dodecyl sulphate with pH 6.75 adjusted using 10 mM KOH. Fluorescence detection set with an excitation/emission of 267/313 nm. The limit of detection (LOD) and lower limit of quantification (LLOQ) for terbutaline was 24.2 and 73.4 µg L⁻¹, respectively.

Statistical analysis

A one-way analysis of variance (ANOVA) test with the application of the Bonferroni correction was used to compare the total emitted dose (TED) at different inhalation flows using SPSS V15.0 (SPSS Inc., Chicago, IL).

A two-way analysis of variance (ANOVA) test was used to compare the urine samples at slow and fast inhalation flows from healthy subjects and COPD patients using SPSS V15.0 (SPSS Inc., Chicago, IL).

Results

In vitro

The TED (*n* = 10 doses) of terbutaline sulphate from the Turbuhaler at different inhalation flows are shown in Table 1. The amounts are expressed as a % of the 500 µg terbutaline sulphate nominal dose.

Table 1 The mean (SD) total emitted dose % of 500 µg terbutaline sulphate at different inhalation flow.

Inhalation flow (L/min)	Volume			
	2 L		4 L	
	One inhalation	Two inhalations	One inhalation	Two inhalations
10	21.4 (13.5)	33.7 (23.6)	34.0 (7.4)	36.4 (11.2)
20	45.5 (7.9)	50.5 (11.5)	48.0 (8.3)	64.9 (2.4)
30	47.5 (6.5)	52.5 (13.9)	56.0 (11.1)	70.5 (4.4)
40	52.3 (6.5)	56.5 (6.1)	64.8 (8.0)	68.9 (6.5)
50	60.8 (11.7)	64.1 (11.5)	72.4 (14.5)	72.5 (7.9)
60	67.0 (4.8)	69.9 (5.3)	76.6 (6.4)	77.3 (3.5)

The TED resulted from the one inhalation and two inhalations increased significantly ($p < 0.05$) with the increase of the inhalation flow at both 2 and 4 L inhalation volumes.

The TEDs resulted from 2 L inhalation volume and one inhalation were significantly lower than from 4 L inhalation volume and one inhalation at all studied inhalation flows ($p < 0.05$).

In vivo

Twelve (six females) healthy non-smoking subjects with a mean (SD) age, weight and height of 29.2 (4.8) years, 66.3 (11.8) kg and 170.5 (7.4) cm, respectively and FEV₁ of 96.1 (3.7) % of predicted completed the DPI flow effect healthy subject study.

Twelve (six females) COPD patients with a mean (SD) age, weight and height of 64.8 (12.4) years, 81.2 (12.7) kg and 167.9 (14.5) cm, respectively and FEV₁ of 46.1 (7.7) % of predicted completed the DPI flow effect patient study.

The mean and individual FEV₁ for healthy subjects and patients are shown in Table 2. The mean (SD) urinary excretion of terbutaline post inhalation of two doses of 500 µg terbutaline sulphate from the Bricanyl Turbuhaler at slow and fast inhalation flows are shown in Table 3 and Figures 1 and 2.

Statistical analysis of the data produced from one inhalation revealed that the mean (SD) terbutaline excreted 30 min and 24 h post start of the inhalation from healthy subjects and COPD patients after slow inhalation flow were significantly lower than after fast inhalation flow ($p < 0.01$). However after two inhalations there was no significant difference between slow and fast inhalation in healthy subjects and COPD patients.

At one inhalation COPD patient excreted significantly lower amount of terbutaline than healthy subject at slow ($p < 0.05$) and fast ($p < 0.01$) inhalation flow. However after two inhalations there was no significant difference between COPD patients and healthy subjects.

In COPD patients after one fast inhalation, the mean (SD) terbutaline excreted 30 min and 24 h post start of the inhalation were significantly lower than after two inhalations ($p < 0.01$). However there was no significant difference in healthy subjects.

Discussion

It has been previously shown that there is a difference in the resistance between the types of dry powder inhaler devices available on the market.¹³ Some have low resistance, others have medium resistance and the remainder have high resistance to inspiratory effort. If the resistance is high, then a greater inspiratory effort is required to generate the same inhalation flow achieved with a lower resistance.

The in vitro results presented here show that the terbutaline sulphate from Turbuhaler has a flow dependent dose emission property after one inhalation at 2 or 4 L inhalation volume, confirming the results of the previously published literatures.^{2,12,14–17} The flow dependent dose emission property could be due to the incomplete de-aggregation of the drug from the device at low flow as was previously shown by de Boer et al. (1996).¹⁸

However this flow dependant dose emission property decreased after two inhalations. Table 1 shows that the two inhalations increased the TED at all inhalation flows and decrease the variation between the TEDs resulted from different inhalation flows. Previous studies have shown that some children,⁵ adult asthmatic^{19,20} and COPD^{21,22} patients have problems achieving the recommended optimal⁴ inhalation flow of 60 L min⁻¹ through a Turbuhaler. Hence to get the most benefit of the inhaled dose it would be better to inhale twice from Turbuhaler mainly for those patients with small inhalation volume and cannot produce a high inhalation flow. However at inhalation flows of 50 and 60 L min⁻¹ there was no significant difference between the TEDs produced from one inhalation and two inhalations. Hence it is very important when using a Tubuhaler to inhale as fast

Table 2 Mean and individual FEV₁% of predicted for each patient and health subject.

Patients						Healthy subject	
Patients code	Day 1	Day 2	Day 3	Day 4	Mean (SD) of each patient	Healthy subject code	FEV ₁
1	45.0	39.0	41.0	55.0	45.0 (7.1)	1	99.0
2	46.0	40.0	35.0	54.0	43.8 (8.2)	2	95.0
3	41.0	55.0	57.0	41.0	48.5 (8.7)	3	99.0
4	43.0	32.0	56.0	56.0	46.8 (11.6)	4	98.0
5	43.0	52.0	34.0	45.0	43.5 (7.4)	5	90.0
6	41.0	55.0	56.0	32.0	46.0 (11.6)	6	99.0
7	48.0	35.0	42.0	53.0	44.5 (7.8)	7	98.0
8	45.0	55.0	42.0	35.0	44.3 (8.3)	8	97.0
9	41.0	55.0	56.0	51.0	50.8 (6.8)	9	92.0
10	44.0	51.0	35.0	41.0	42.8 (6.7)	10	99.0
11	47.0	53.0	55.0	56.0	52.8 (4.0)	11	89.0
12	46.0	51.0	40.0	40.0	44.3 (5.3)	12	98.0
Mean (SD)	44.2 (2.4)	47.8 (8.7)	45.8 (9.4)	46.6 (8.6)	46.1 (7.7)	Mean (SD)	96.1 (3.7)

Table 3 Mean (SD) urinary excretion of terbutaline 30 min and over the first 24 h post dosing of two 500 µg terbutaline sulphate doses from the Turbuhaler using slow and fast inhalation flows [expressed in µg] (*n* = 12).

	Inhalation flow	Healthy subjects		COPD patients	
		30 min	24 h	30 min	24 h
One inhalation	Slow	4.9 (3.9)	222.2 (191.3)	4.2 (2.8)	180.5 (102.8)
	Fast	15.9 (8.2)	502.5 (194.6)	6.8 (5.9)	269.7 (215.2)
Two inhalations	Slow	14.4 (7.2)	495.3 (191.6)	12.7 (6.3)	475.6 (187.7)
	Fast	17.4 (8.9)	531.6 (199.8)	16.4 (8.5)	516.8 (199.9)

and deep as possible. This fast inhalation flow would overcome the lung volume limitation of some patients.

This is consistent with the most desirable inhalation flow for use with the Turbuhaler which has been reported to be 60 L min⁻¹,^{3,23} and the patient information leaflet which instructs the patients to inhale as deep and hard as they can during inhalation. When patients use the recommended inhalation technique for a Turbuhaler and inhale as deep and hard as they can, then their inhalation flow through this device will determine the amount deposited in their lung. An addition to the patient information leaflet of the Turbuhaler can be recommended, to 'inhale twice when taking each dose', as this may increase the dose delivered to the lung.

Previously the TED and the fine particle dose (FPD) were determined from terbutaline sulphate Turbuhaler over the inhalation flow rates of 10–60 L min⁻¹ with a 4 L inhalation volume. At inhalation flow rate of 10, 20, 30, 40, 50 and 60 L min⁻¹ the mean (SD) FPD were 1.6 (0.8), 1.9 (0.7), 5.9 (2.5), 12.8 (4.3), 24.2 (1.9) and 36.5 (5.1) % of the 500 µg terbutaline sulphate nominal dose, respectively.²⁴ This study showed that the terbutaline sulphate from Turbuhaler has a flow dependent dose emission property and flow dependent fine particle dose characteristic. The TED and FPD were significantly increased with the increase of

the flow (*p* < 0.001). However the flow had a more pronounced effect on the FPD than the emitted dose, thus, a faster inhalation increases the respirable amount more than it increases the emitted dose.²⁴

The flow dependent dose emission characteristics have been reported from the Turbuhaler containing budesonide,^{2,16} salbutamol,¹⁷ terbutaline^{14,15} and a combination of budesonide and formoterol.¹² However those studies were made using an inhalation flow above 30 L min⁻¹ and one inhalation only.

The data represented here suggests that below 30 L min⁻¹ the TED falls off very sharply after one inhalation with 2 or 4 L inhalation volumes. This suggests that 30 L min⁻¹ is the minimum flow that should be used through the terbutaline sulphate Turbuhaler. However the TED increased even at inhalation flows lower than 30 L min⁻¹ when using two inhalations.

A novel pharmacokinetic method that have been previously developed for Salbutamol⁷ and validated for terbutaline⁸ was used here to compare the different inhalation maneuvers. As mentioned before, the previously validated terbutaline pharmacokinetic method had shown that the amount of terbutaline excreted in urine 30 min post dosing is an index of the amount of terbutaline deposited in the

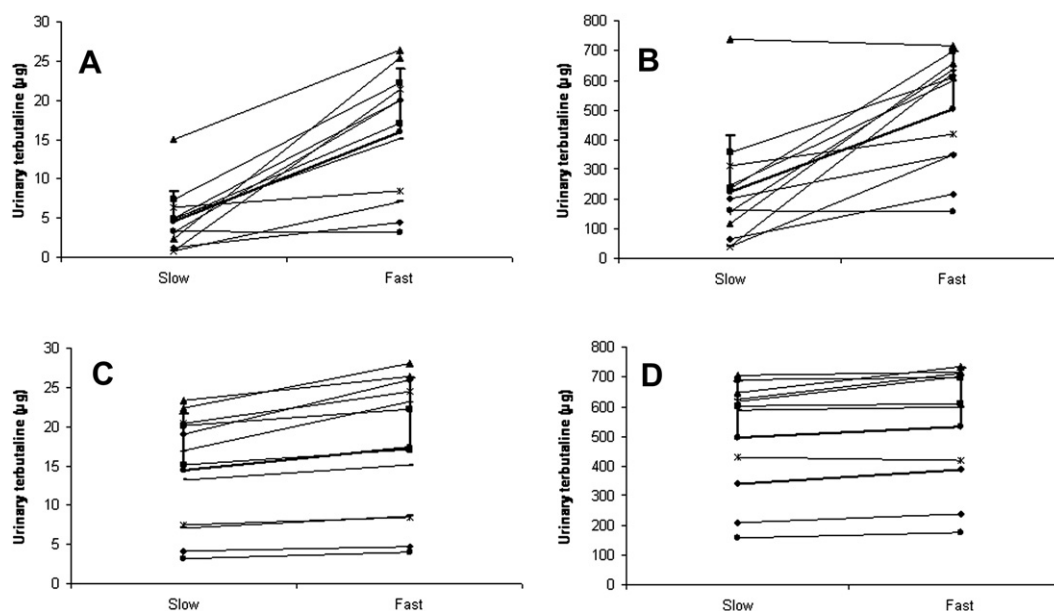


Figure 1 Mean (SD) [*n* = 12] and the individual amounts of urinary terbutaline excreted from healthy subjects (A) 30 min post one inhalation; (B) over the first 24 h post one inhalation; (C) 30 min post two inhalations; and (D) over the first 24 h post two inhalations of two doses of 500 µg terbutaline sulphate dosing from the DPI using a fast and slow inhalation flows.

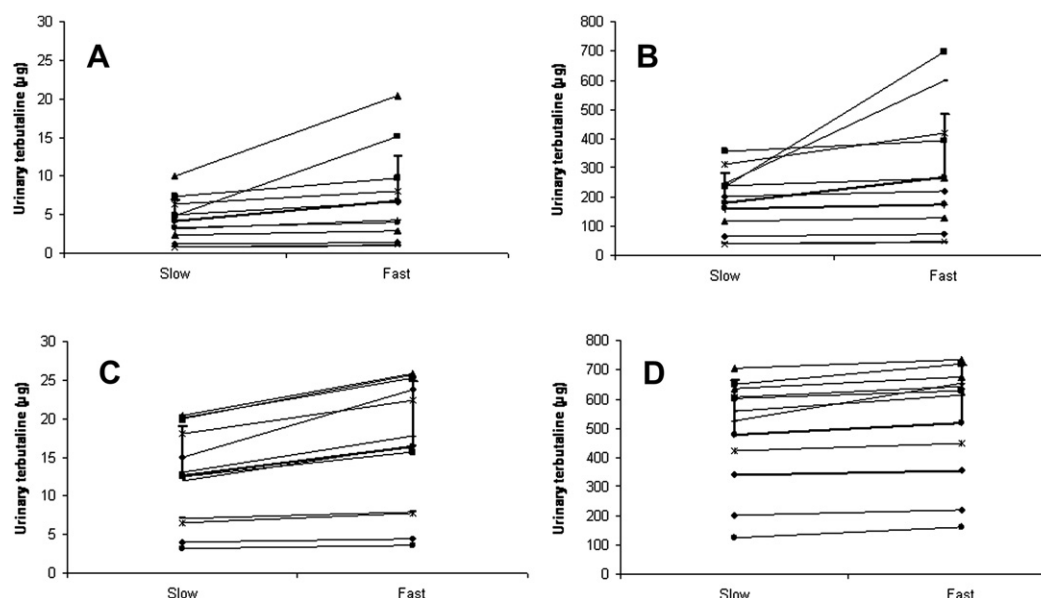


Figure 2 Mean ($n = 12$) and the individual amounts of urinary terbutaline excreted from COPD patients (A) 30 min post one inhalation; (B) over the first 24 h post one inhalation; (C) 30 min post two inhalations; and (D) over the first 24 h post two inhalations of two doses of 500 µg terbutaline sulphate dosing from the DPI after using a fast and slow inhalation flows.

lung (lung bioavailability of inhaled terbutaline) and the amount of terbutaline cumulatively excreted in the urine post 24 h is an index of the systemic bioavailability of the inhaled terbutaline.

The amount excreted 30 min and 24 h post dosing using slow and fast inhalation flows after one inhalation from healthy subject and COPD patients confirm the flow dependent dose emission property of the Turbuhaler. This was expected from the previously shown in vitro FPD²⁴ and TED flow dependant. The results indicate that the fast inhalation flow resulted in a significantly higher amount of urinary terbutaline excretion 30 min and 24 h post dosing than slow inhalation ($p < 0.01$), hence better lung deposition and higher systemic bioavailability. Two Gama scintigraphy studies^{3,4} have shown similar results that support the inhalation at fast inhalation flow from a Turbuhaler.

At fast inhalation flow the amount of terbutaline excreted 30 min and 24 h post dosing were significantly higher in health volunteers than in COPD patients ($p < 0.001$) and the same were observed at slow inhalation flow ($p < 0.05$). Since it was previously demonstrated that Turbuhaler functions well in COPD patients, in stable disease,²⁵ moderate to severe patients^{26,27} and in patients with exacerbations,²⁸ the difference between the healthy subjects and the COPD patients could be due to inhalation volume. The inhalation volume that can be produced by the healthy subject is much higher than that produced by COPD patient⁶ which is an important factor for the de-aggregation of the terbutaline particles from Turbuhaler.¹⁸

However after two inhalations there was no significant difference in the amount excreted 30 min and 24 h post dosing between fast and slow inhalation or healthy volunteers and COPD patients. This is similar to the effect of the two inhalations on the TED shown above especially at inhalation flow 30 and 60 L min⁻¹ which are the flow used for the in vivo test. This support the use of two inhalations when using the Turbuhaler to increase the dose delivered. The use of the second

inhalation adds a new effort to de-aggregate the particles of the drug in the Turbuhaler hence resulting in better deposition.

Nevertheless, the healthy subjects excreted similar amounts of terbutaline post one and two inhalations using fast inhalation. This is similar to the in vitro TED at high inhalation flow (50 and 60 L min⁻¹). This suggests that it would be unnecessary to inhale twice if subject can inhale at fast inhalation flow with large inhalation volume. Though, for a patient with a low inspiratory effort and/or small inhalation volume it would be better to inhale twice from a DPI with a high resistant like Turbuhaler.

A study by Derom et al. (2007) showed that the severity of COPD does not seem to affect the lung deposition of drugs inhaled via Turbuhaler.²⁹ Though the study was performed on COPD patients only and did not contain any healthy subjects who have different lung calibres. Also they used one inhalation flow only which was 60 L min⁻¹.

It have been previously shown that for some dry powder devices such as the Accuhaler and Easyhaler the effect of the inhalation flow is low whilst it is greater for the Turbuhaler.² In addition, the dose delivered from the Turbuhaler was generally less than the labeled amount and was dependent on the inhalation flow.² An optimal inhalation flow may have to be achieved through DPIs with high resistance to be used effectively.^{2,30} Therefore, Turbuhaler or any DPI with a high resistant might be unsuitable for patients with limited inspiratory effort and inhalation volumes. If those patients have to use Turbuhaler, it would be better to advice them to inhale each dose twice and as deep and fast as possible.

Conclusion

The in vitro flow dependent dose emission that has been previously demonstrated for terbutaline sulphate in the

Turbuhaler above 30 L min⁻¹ is more pronounced below this flow. The flow dependent dose emission results highlight the need for the Pharmacopoeias to use a variety of inhalation flows and volumes rather than one that is equivalent to pressure drop of 4 kPa and 4 L inhalation volume. The results are consistent with the most desirable inhalation flow for use with the Turbuhaler which has been reported to be 60 L min⁻¹.

It is essential to inhale twice and as hard and deep as possible from each dose for patients with limited inhalation volumes and poor inspiratory efforts as they may not receive much benefit from one inhalation. Although it is possible to identify those patients using an In-Check Dial³¹ it may be of some value to encourage all patients to inhale more than once from one dose.

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Conflict of interest statement

No competing financial interests exist.

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